Millipore and Cytomyx Ltd.

Cytomyx Ltd., a wholly owned subsidiary of Cytomyx Holdings Plc. (AIM: CYX), is now part of Millipore. The Cytomyx Ltd. team brings a globally recognized leadership in ion channel cell line development and specialized electrophysiology to our array of drug discovery services.

We now offer the world's largest portfolio of cell lines expressing biologically-relevant ion channels alongside our world class kinase and GPCR lines. Millipore can now serve you with the highest quality products and services for the three largest drug discovery classes.

PrecisION ion channel cell line product offering

Visit www.millipore.com/ionchannels for a complete list of our PrecisION ion channel products or email ionchannels@upstate.com for more information.

	Product Name	Alias	Cat. No.
	hERG-CHO	ERG1, KCNH2, Kv11.1	CYL3002
New	hERG-CHO K1	ERG1, KCNH2, Kv11.1	CYL3038
New	hERG-HEK	ERG1, KCNH2, Kv11.1	CYL3006
	hERG-HEK	ERG1, KCNH2, Kv11.1	CYL3039
	hKv1.1-CHO	KCNA1	CYL3014
	hKv1.2-CHO	KCNA2	CYL3015
	hKv1.3-CHO	KCNA3	CYL3016
	hKv1.4-CHO	KCNA4	CYL3017
	hKv1.5-CHO	KCNA5	CYL3018
	hKv1.6-CHO	KCNA6	CYL3019
New	hKv1.7-CHO	KCNA7	CYL3020
New	hKv1.8-CHO	KCNA10	CYL3021
New	hKv2.1	KCNB1	CYL3022
	hKv4.2/KChIP2-CHO	KCND2	CYL3026
	hKv4.3/KChIP1-CHO	KCND3	CYL3027
	hKCNQ1/minK-CHO	KvLQT1/KCNE1	CYL3007
	hNav1.1-HEK	SCN1A, BRAIN I	CYL3009
New	hNav1.2-CHO	SCN2A, BRAIN II	CYL3023
	hNav1.3-CHO	SCN3A, BRAIN III	CYL3003
New	hNav1.4-HEK	SCN4A, SKM1	CYL3024
	hNav1.5-HEK	SCN5A, SKM2	CYL3004
	hNav1.6-HEK	SCN8A, PN4, BRAIN VI	CYL3010
	hNav1.7-HEK	SCN9A, PN1	CYL3011
	hHCN4-CHO		CYL3012
New	hGRIK2-HEK	GluR6	CYL3049
New	TRPM8	Trp-p8	CYL3048

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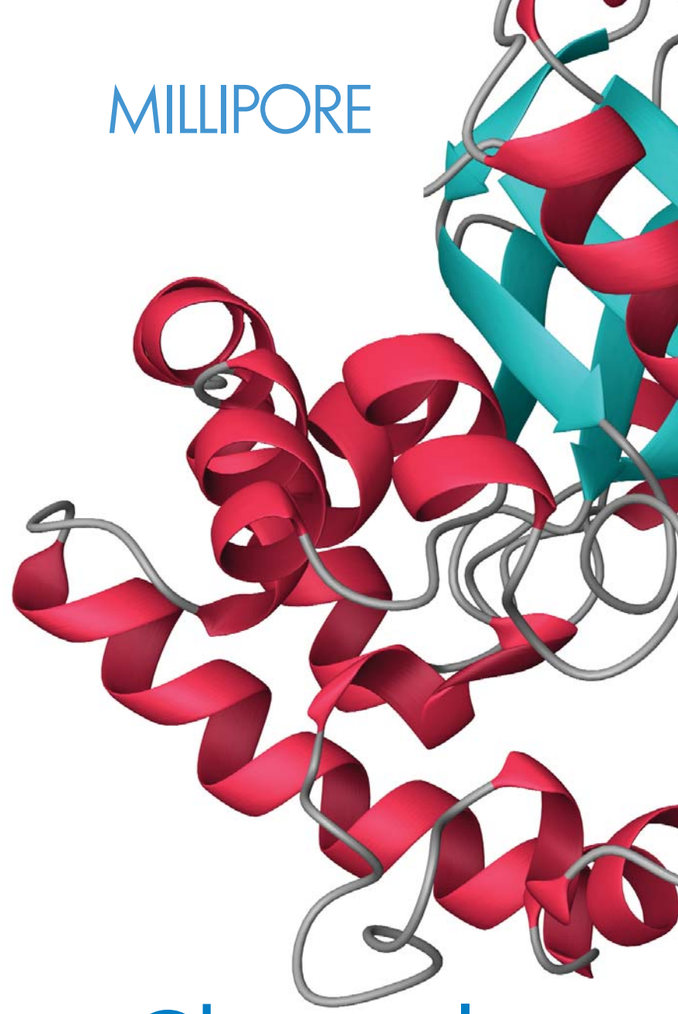


Ion Channels

Lead Identification, Selectivity and Profiling

Upstate
Ion Channel Discovery Group
(formerly Cytomyx Ltd.)
CYTOMYX

upstate
now part of Millipore

PrecisION™ Ion Channels

Lead Identification, Selectivity and Profiling

High quality, functionally validated ion channel cell lines

Ion channels are well known for having a critical role in nerve and muscle function and consequently have a key function in pain, CNS and the heart. Drugs that modulate ion channels have been investigated in therapeutic areas, such as neuropathic pain, cardiac arrhythmia, hypertension, local anaesthesia, stroke, Parkinson's, obesity, epilepsy, diabetes and depression.

Historically, ion channels have been under exploited as drug targets primarily due to the lack of functional high throughput screening technologies. Over recent years, there has been considerable progress in this important area. However, now there is a requirement for high quality research tools that will allow the full benefit of the new screening technologies to be realized. Millipore offers a portfolio of ion channel cell lines to meet these new and evolving needs in the drug discovery industry.

Upstate® PrecisION ion channel cell lines from Millipore are available off the shelf. These cell lines are fully validated using electrophysiology, stable (>25 passage) and licensed for drug discovery research. The objective is to provide the pharmaceutical industry with a range of ion channel cell lines to support drug discovery, lead optimization and safety pharmacology functions.

Upstate PrecisION ion channel advantages

- **Full functional validation** by biophysical and pharmacological methods
- **Validated utilizing conventional patch clamp and IonWorks™ HT** to meet your HTS needs
- **Developed using superior vector technology** giving increased stability and expression
- **An extensive portfolio of cell lines** is available for selectivity screening and cardiac liability profiling

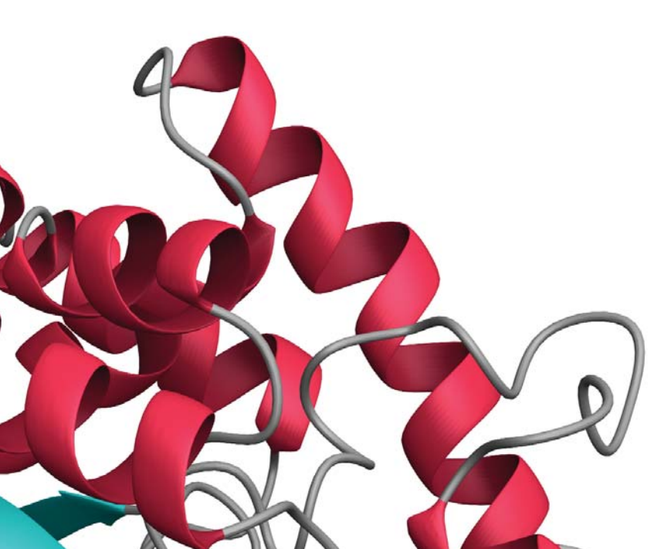


Figure 1A: A typical voltage protocol used to assess block of Nav1.5 currents on IonWorks HT

Since most clinically available sodium channel blockers are use-dependent, multi-pulse voltage protocols can be implemented to assess the extent of block of the 1st pulse compared to subsequent pulses. In the example shown, 5 pulses to 0 mV are applied from a holding potential of –80 mV (inter pulse interval is 100 ms) before and after compound addition, and the extent of block is measured for both the 1st and 5th pulse.

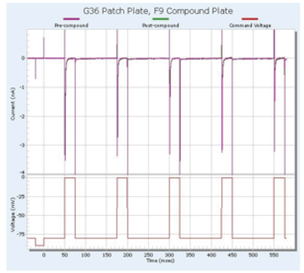


Figure 1B: Using a 5 pulse voltage protocol to measure use-dependent block of lidocaine on IonWorks HT

Using the protocol described in Figure 1A, lidocaine blocks the 5th pulse to a much greater extent than the 1st pulse for a given concentration of compound. The IC_{50} value shifts approximately 10-fold when comparing the amount of block observed on the 1st pulse with the amount of block observed on the 5th pulse (i.e. lidocaine shows marked use-dependence).

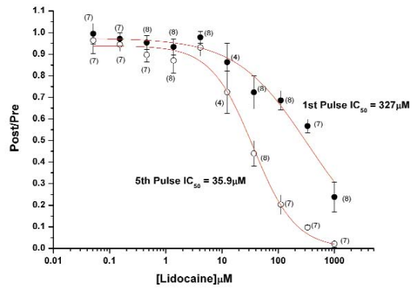
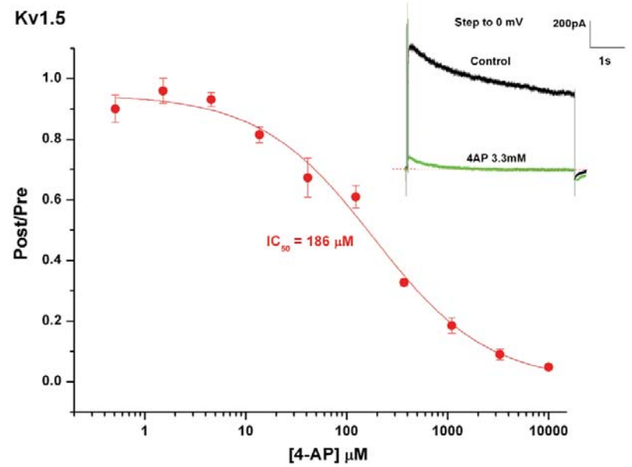


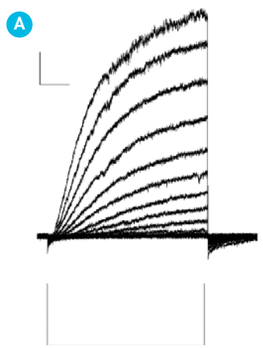
Figure 2: The effect of 4-AP on Kv1.5 channels using IonWorks HT



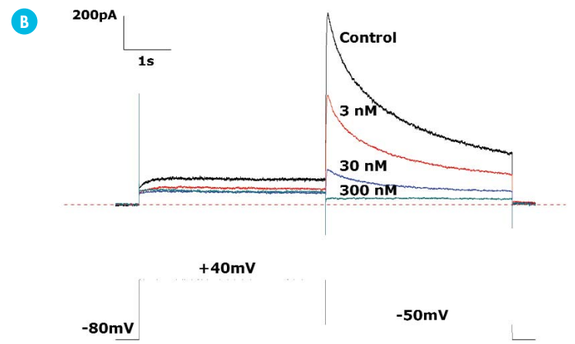
4-Aminopyridine (4-AP) dose-dependently inhibited Kv1.5 currents evoked by stepping the membrane potential from –80 mV to 0 mV for 4 seconds. Currents were measured at the end of the 4 second depolarization before (Pre) and after (Post) a 10 minute incubation with compound and the ratio Post/Pre plotted against concentration to give a dose response curve with an estimated IC_{50} of 186 mM. A typical effect of a high concentration of 4-AP (3.3 mM) is shown in the inset. This shows complete blockage of the Kv1.5 outward current.

Figure 3: The major cardiac potassium ion channels responsible for ventricular repolarization

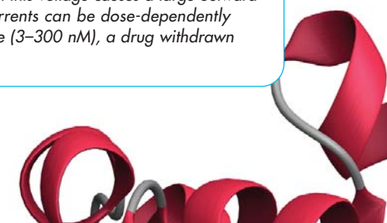
hERG (CYL3039) and KCNQ1/minK. The link between blockade of the hERG channel by drugs, QT prolongation and Torsades de Pointes (TdP) is now well established. The hERG cell line (CYL3039) has been validated using automated electrophysiology as well as conventional patch clamp techniques. In addition, Millipore can also offer cell lines for the majority of other ion channels involved in the cardiac ventricular action potential. One such ion channel is KCNQ1/minK that, along with hERG, is responsible for the repolarizing phase of the action potential. Typical hERG and KCNQ1/minK currents are shown at right (A).



(A) KCNQ1/minK currents evoked by stepping from a holding potential of –80 mV to test potentials ranging from –60 to +60 mV. The current activates with a delay and becomes progressively larger with increasing depolarization with no discernable inactivation (calibration bars 200 pA, 1s).



(B) In contrast, hERG currents rapidly inactivate on stepping to depolarized potentials (e.g., +40 mV). Upon stepping back to –50 mV, the channels recover from inactivation. A significant number opening prior to deactivation at this voltage causes a large outward tail current (control in figure). These hERG tail currents can be dose-dependently blocked by the gastrointestinal prokinetic, Cisapride (3–300 nM), a drug withdrawn from the market, due to increased incidence of TdP.



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